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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/155,452	10/23/1998	RHONA HARRIET BORTS	263/PPIR1165	8673

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/155,452	Borts et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 4, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11 and 13-35* is/are pending in the application.

4a) Of the above, claim(s) *14, 15, 18-20, 24-29, and 32-34* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11, 13, 16, 17, 21-23, 30, 31, and 35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Prosecution Application

The request filed on June 14, 2001, paper number 15, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/155,452 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application is a 371 National stage filing of PCT/GB97/00875, filed March 27, 1997, which claims benefit to provisional application 60/014,490, filed April 1, 1996.

Applicants amendment filed January 4, 2002, paper number 18, has been received and entered. Claim 12 has been canceled. Claims 11, 13, 16-18 and 22 have been amended. Claims 23-35 have been added. Claims 11, 13-35 are pending.

Election/Restriction

Claims 11, 13-35 are pending. Claims 14, 15, 18, 19-20, 28, 29, 32-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species other than animals, there being no allowable generic or linking claim. Specifically, each of these

claims are directed to non-elected species of unicellular organism or plants. Election was made without traverse in Paper No. 10. Additionally, newly submitted claims 24-27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 24 and 25 are directed to a method of obtaining hybrid DNA by isolating hybrid DNA from a eukaryotic cell, and claims 26 and 27 are directed to making proteins from hybrid DNA. Each of the methods are drawn to methods which is different than the elected invention of affecting meiotic recombination *in vivo*. Each of the newly claimed methods requires the use of different materials, different method steps and result in material different outcomes, and would require a separate search and consideration of each of the inventions which would not be required for the elected invention. Further, each of the newly claimed methods would be classified in a different class/subclass than the elected invention.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 11, 13, 16, 17, 21-23, 30, 31 and 35 are currently under examination as they are directed to the elected species of animals.

Claim Objections

Claims 11, 13, 16, 17, 21-23, 30, 31 and 35 are objected to because of the following informalities: In response to the restriction requirement Applicants have elected for examination claims encompassing animals. Presently, the claims only recite eukaryotic cells which is much broader than animal cells, and encompass non-elected inventions such as plants and yeast. The claims should be amended to reflect the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 16, 17 and 21 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Applicants note the amendments to the claims and argue that the present claims are limited to practice in eukaryotic cells and not whole animals. See Applicants amendment, bottom of page 9.

The specification teaches that homologs of bacterial mismatch repair genes 'have been identified in organisms ranging from yeast to man' (page 2, lines 1-3). Further, the specification specifically states that it 'envisages the possibility of performing such recombinations in bacteria, yeasts, plant or animal cells (page 3, lines 4-5). Additionally, original claim 1 encompassed a process for meiotic recombination *in vivo* in eukaryotic cells (page 28). Further, the original dependent claims clearly recite the method steps contemplated in the newly added claims. Meiosis and meiotic recombination occurs during the production of haploid gametes (page 2) and in animals, meiosis only occurs only in the germ line cells. Clearly, the specification teaches that mismatch repair enzymes exist in 'yeast to man' and it was contemplated that observations in the bacterial system could be extended to eukaryotic cells. Since the disclosure as filed supports the instantly pending claims, the new matter rejection of claims 11, 12, 16, 17 and 21 is withdrawn.

Claims 11, 13, 16, 17, 21-23, 30, 31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The present invention encompasses a method of enabling meiotic recombination *in vivo* of partially homologous DNA sequences in an animal comprising: 1) genetically or physiologically manipulating cells to render defective the enzymatic mismatch repair system of said cells wherein said cells contain partially homologous DNA sequences, and 2) culturing said manipulated cells under conditions to effect meiotic recombination *in vivo*. Further, claim 22 encompasses making a hybrid animal cell wherein two populations of cells are cultured in vivo under conditions to effect meiotic recombination. The specification provides working examples of this method in yeast cells wherein the mutS and mutL genes have been inactivated by genetic alteration. The specification states "Although the specification envisages the possibility of performing such recombinations in bacteria, yeasts, plant or animal cells, in fact the experimental

data provided only demonstrate such recombinations in bacteria..." (page 3, lines 3-6). Further, the specification in review of the art only teaches miss-match repair genes from lower eukaryotes, and provides no specific teaching of homologues in animals or any specific methods for isolating these gene from animal cells. Importantly, no guidance is provided in the specification teaching one of ordinary skill in the art how to employ the methodology for use in animal cells *in vivo* as demonstrated in yeast in the working examples.

Applicants argue that based on the teaching of the specification and the knowledge in the art, a skilled artisan can practice the claimed process. Further, Applicants note that references will be submitted demonstrating that one of skill in the art can practice various embodiments of the claims. See Applicants' amendment, top of page 10. Applicants' arguments have been fully considered but not found persuasive. First, it is noted that Applicants have not supplied any references demonstrating that given the guidance in the present specification one of skill in the art could practice the claimed methods *in vivo* in animals. Second, in review of the relevant art at the time of filing, it is noted that mammalian homologues of MLH1,MSH2, PMS2 genes were known. For example, Edelmann *et al.* (Cell, 1996) teach that mammalian mismatch repair genes were known, but their roles in mismatch repair in mammals were not defined (page 1125, bottom of second column). In animals *in vivo*, the process of meiosis only occurs in the germ cells and results in the halving of chromosome number during the formation of gametes. The specification provides working examples of yeast in which various mismatch repair enzymes have been rendered inactive. The specific results presented demonstrate that inactivating

mismatch repair enzymes allows the yeast to proceed through meiosis and produce viable haploid spores which subsequently can be used to form diploid cells (page 22, Table II-haploid spores and page 26, Table V-hybrid diploid cells). However, unlike in yeast, Edelmann *et al.* teach when the MLH1,MSH2, PMS2 are mutated in mice *in vivo*, each of the mice are sterile (pages 1125-1126, bridging paragraph). As specifically demonstrated in the characterization of the MLH1 knockout mice, the lack of mismatch repair gene function in mice results meiotic arrest (page 1128, second column), not meiotic recombination. Furthermore, it is noted by Edelmann *et al.* that after arrest, the cells do not progress any further indicating that hybrid cells could not be formed if they contained these alterations (page 1128, second column). Disruption of other mismatch repair genes continue to show a similar phenotype when disrupted in mice, for example, Lipkins *et al.* (Nature Genetics, 2002) teach that a disruption in the mismatch repair gene MLH3 in mice resulted in meiotic arrest. Clearly both yeast and mammals have homologs of mismatch repair genes such as the MLH1, MSH2, PMS2 genes, and these genes are involved somehow in the mismatch repair system, however, contrary to the requirement of the present methods, mutating the genes in mismatch repair in mammals results in the arrest of meiosis and not in increased recombination between non-homologous sequences.

The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

> enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The specification teaches that in 'eukaryotes, the enzymatic mismatch repair systems are more complex than in prokaryotes' (page 3, lines 9-10). Further, it is acknowledged that 'the enzymatic mismatch repair systems involved in meiosis are to some extent different from those mitosis' and that it was 'not predictable that the techniques generally described' in the art could successfully be applied to eukaryotic cells undergoing meiosis (page 3, lines 10-14). In the instant case, at the time of filing the disruption of the yeast mismatch repair gene homologs in mammals resulted in an arrest in meiosis indicating that the methods demonstrated in yeast would not simply extend to more complex systems. As acknowledged by the specification, the art teaches that in mammalian systems the role of the mismatch repair genes becomes more complicated than that disclosed for the single cell organism such as the yeast. For example, Edelmann *et al.* teach that disruption of MLH1 resulted in sterility in both male and females, while disruption of either MSH2 and PMS2 resulted in only male sterility (page 1125, bottom of second column). Contrary to observations in yeast, Moens *et al.* (J Cell Sci, 2001)teach that the mismatch repair enzyme MLH1 'is **essential** for reciprocal recombination in the mouse' (emphasis added, page 1611, summarized in abstract). Further, the art teaches that the proteins of the mismatch repair genes in mammals appear to function in complexes and vary in function when compared to the properties of homologs in bacteria. For example, Moens *et al.* teach that

MLH1 co-localizes with MSH4, however the role of MLH1 and the role of MLH1/MSH4 is speculative (page 1620, top of second column). In another example, Santucci-Darmanin *et al.* (FASEB, 2000) more clearly demonstrate that MLH1 and MSH4 interact to form a complex during meiosis in mammals, however it is taught that other factors are likely to interact with the complex and play a functional role in meiosis *in vivo* (page 1546, middle of first column). Each Moens *et al.* and Santucci-Darmanin *et al.* demonstrate the multicomponent nature of the repair systems in mammals, and provide support for the added complexity of recombination and repair during meiosis in mammals as compared to single cell organisms. Therefore, while the present specification provides working examples that disruption of mismatch repair genes in yeast will allow recombination between non-homologous sequences of two different strains of yeast, the art teaches that the properties observed in yeast do not simply extend to higher eukaryotes such as mammals. Furthermore, while mismatch repair genes from yeast and mammals appear to be homologs of each other at a structural level, the demonstration of the complex interaction of these gene products in mice compounded with the complexity of the physiology of a multicellular organism as evidenced in knock-out mice by the variability in transgene affect observed among the various known mismatch repair genes, clearly demonstrates that the observations of single cell organism such as yeast is not simply applicable to expectations in higher eukaryotic cells *in vivo*. The specification provides no guidance on how to practice the instantly claimed methods for affecting meiosis in animals *in vivo*, nor does it provide any guidance on recombining the resulting haploid cells to produce a hybrid diploid. In view of the

substantial difference and consequences of disrupting mismatch repair genes in yeast versus animals, and the lack of any guidance to practice the instantly claimed methods in animals, it would have constituted an undue burden to establish specific methodology to practice the methods as claimed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 13, 16, 17, 21-23, 30, 31 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 11, 22 and 23 are unclear and indefinite in the recitation 'under conditions' because the term is not specifically described in the specification nor are any specific conditions for culturing cells clearly set forth. The claims are unclear because the metes and bonds of the conditions encompassed by this term are not defined. Dependent claims are included in the basis of the rejection because they fail to further define the metes and bounds of the conditions encompassed by the claims.

Claim 13 is unclear and confusing because it does not appear to further limit claim 11 from which it depends. The two different groups of cells, a and b, in claim 13 lack sufficient antecedent basis in claim 11. Further, practicing claim 13 results in a diploid cell, however independent claim 11 provides no support for the use of a diploid cell, or how two separate cell groups would be used in the method.

Claim 23 is unclear and indefinite in the term of 'a hybrid eukaryotic specie' because the term is not specifically defined in the specification, and the nature of the hybrid specie are not clearly defined by the method steps in the claims. First, the claim is unclear to whether 'specie' refers to different individuals or to different taxonomic categories. Second, if it refers to different taxinomic groups, it is unclear how varied of species the claims encompass. For example, does it encompass making hybrid yeast-human or only yeast-yeast. It is noted that the claim recites that the cells have up to 30% of base pair mismatch, however it is not clear if this is in reference to the whole genome of only selective sequences. Dependent claims are included in the basis of the rejection because they fail to further clarify the nature of the resulting hybrid cell or the scope of the specie of cell used.

Conclusion

No claim is allowed. The claims are free of the art of record because the art does not teach or suggest that disruption of the enzymatic mismatch repair system in animals would enable meiotic recombination.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

RAM R. SHUKLA, PH.D
PATENT EXAMINER